amended, claims 7, 9, and 14 to 31 have been cancelled, and new claims 32 to 42 have been added, herein. Following entry of the amendments, claims 1 to 6, 8, 10 to 13 and 32 to 42 will be pending in the application.

Claim Objections

Claims 2, 11, and 13 have been objected to for allegedly containing subject matter drawn to a non-elected invention. Claims 2 and 13 have been amended to delete the non-elected subject matter; specifically, claims 2 and 13 have been amended to no longer recite that the compound is a protein. Claim 11, however, does not contain non-elected subject matter. According to the Office Action dated November 5, 2002, the non-elected subject matter of Group II relates to methods of introducing a compound into a cell that expresses costimulatory molecules *in vitro* and *in vivo*, wherein the ***compound*** is a protein. In contrast, claim 11 recites "[t]he method of claim 1 wherein the ***particle*** is a viral particle, a protein complex, a liposome or a cationic amphiphile/DNA complex." (emphasis added). Claim 11, therefore, does not contain non-elected subject matter in which the ***compound*** is a protein, but, rather, recites that the ***particle*** may be a protein complex. Accordingly, Applicants respectfully request withdrawal of the objections to claims 2, 11, and 13.

Alleged Indefiniteness

Claims 1 to 6 and 8 to 13 have been rejected under 35 U.S.C. § 112, second paragraph as indefinite because the claims allegedly "do not recite proper routes of delivery in an *in vivo*

setting, it is unclear how the non-cellular particle reach the targeting cell *in vivo*." (Office Action dated March 1, 2002, page 9). Applicants respectfully traverse the rejection because the claims convey a clear and definite meaning to those skilled in the art.

"The test for definiteness is whether one skilled in the art would understand the bounds of the claim when read in light of the specification. If the claims read in light of the specification reasonably apprise those skilled in the art of the scope of the invention, § 112 [second paragraph] demands no more." *Miles Laboratories, Inc. v. Shandon Inc.*, 997 F.2d 870, 875 (Fed. Cir. 1993).

Those skilled in the art would readily understand the scope of the subject matter encompassed by the claims upon review of the present claims in light of the specification. The stated bases for the instant rejection do not involve objections based upon the definiteness of the claim language, but, rather, address the mechanism by which the claimed methods achieve their intended results. Accordingly, Applicants believe that the instant rejection for alleged indefiniteness is improper, and request withdrawal thereof.

Claim 4 has been rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite for recitation of "a nucleotide sequences" because "a" is singular and "nucleotide sequences" is plural. Without conceding the correctness of the rejection and to advance prosecution, claims 4, 5, and 6 have been amended to replace "sequences" with "sequence." The rejection has been obviated, and Applicants request withdrawal thereof.

Claim 8 has been rejected under 35 U.S.C. § 112, second paragraph as indefinite because recitation of "a macrophage cell" is allegedly redundant. Without conceding the

correctness of the rejection and to advance prosecution, claim 8 has been amended to delete the word "cell." The rejection has been obviated, and Applicants request withdrawal thereof.

Alleged Lack of Written Description

Claims 1 to 6 and 8 to 13 have been rejected under 35 U.S.C. § 112, first paragraph for lack of written description because the specification allegedly fails to adequately describe the compounds and costimulatory molecules embraced by the claims. Applicants respectfully traverse the rejection because the specification describes the costimulatory ligands embraced by the present claims and describes a representative number of species of the compounds embraced by the claims.

"The purpose of the adequate written description requirement is to ensure that the inventor had possession of the claimed subject matter at the time the application was filed. If a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, then the adequate written description requirement is met." *In re Alton*, 76 F.3d 1168, 1175, 37 U.S.P.Q.2d 1578, 1584 (Fed. Cir. 1996). A genus may be adequately described through description of a representative number of species that comprise the genus. *Regents of the Univ. of Calif. v. Eli Lilly and Co.*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

Preliminarily, to further clarify the claimed subject matter, claims 1 and 13 have been amended to recite that the costimulatory ligand comprises CD28 or a portion thereof.

Support for the amendments is found in the specification, at, for example, page 24, lines 1 to 16.

The specification describes the costimulatory ligands embraced by the claims. The amended claims recite that the costimulatory ligand comprises CD28 or a portion thereof. The specification teaches that the costimulatory ligand specifically binds to a costimulatory molecule. See page 23, lines 18 to 22 of the specification as filed. The specification further teaches that the costimulatory ligand can be a natural ligand of the costimulatory molecule or can be a fusion protein that comprises a natural ligand of the costiumlatory molecule, or a functional fragment thereof. *Id.* The specification lists the natural ligands of numerous costimulatory molecules and states that CD28 is a natural ligand of CD80. See page 24, lines 1 to 10 of the specification as filed. The specification thus teaches that CD28 and fragments thereof comprise the costimulatory ligand, and, therefore, adequately describes the costimulatory ligands encompassed by the present claims.

In addition, the specification describes a representative number of species of the compounds that can be introduced into cells according to the methods defined by the present claims. For example, the specification teaches that such compounds can be genetic constructs that include nucleotide sequences encoding peptides comprising an epitope identical to, or substantially similar to, an epitope displayed on a pathogen antigen such as macrophage colony-stimulating factor, chemokine (C-Cmotif) receptor 5, monocyte chemoattractant protein, pFLT3, pFLT3LG, 4-1BB, 4-1BBL, RANTES, CCR1/MIP1R, CCR5, CCR2, CCR3, CD40 ligand, CD86, CD80, CD40, LFA-3, ICAM1, and CD28. See page 8, line 26 to page

9, line 9 and page 33, line 8 to page 37, line 16 of the specification as filed. The specification further teaches that the compounds that can be introduced into cells according to the methods defined by the present claims can be genetic constructs that include nucleotide sequences encoding proteins associated with a hyperproliferative disease, including proteins encoded by oncogenes such as *myb*, *myc*,*fyn*, *bcr/abl*, *ras*, *src*, P53, *neu*, *trk*, and EGRF; variable regions of antibodies made by B cell lymphomas; variable regions of T cell receptors of T cell lymphomas; and proteins found at higher levels in tumor cells, including the protein recognized by monoclonal antibody 17-1A and folate binding proteins. See page 9, line 14 to page 10, line 3.

The specification also teaches that the compounds that can be introduced into cells according to the methods defined by the present claims can be genetic constructs that include nucleotide sequences encoding proteins associated with T-cell mediated autoimmune diseases such as rheumatoid arthritis (RA), multiple sclerosis (MS), and scleroderma. See page 10, line 4 to page 11, line 3 of the specification as filed. Such compounds, according to the specification, include DNA constructs encoding at least one of the variable regions of the T cell receptors involved in RA, including Vβ-3, Vβ–14, Vβ–17, and Vα–17; DNA constructs encoding at least one of the variable regions of the T cell receptors involved MS, including Vβ-7 and Vα-10; and DNA constructs encoding at least one of the variable regions of the T cell receptors involved in scleroderma, including Vβ-6, Vβ-8, Vβ-14, Vα-16, Vα-3C, Vα-7, Vα-14, Vα-15, Vα-16, Vα-28, and Vα-12. *Id.*

The specification also teaches that the compounds that can be introduced into cells

according to the methods defined by the present claims can be genetic constructs that include nucleotide sequences encoding proteins associated with B-cell mediated autoimmune diseases, such as Lupus. See page 11, line 9 to page 12, line 3 of the specification as filed. Such compounds, according to the specification, include DNA constructs encoding the variable region of anti-DNA antibodies associated with Lupus. *Id.*

The specification further teaches that the compounds that can be introduced into cells according to the methods defined by the present claims can be genetic constructs that include nucleic acid molecules that serve as replacement copies of defective, missing, or non-functioning genes. See page 12, line 4 to page 13, line 16 of the specification as filed. Such nucleic acid molecules, according to the specification, include genes encoding dystrophin or functional fragments thereof, genes that compensate for the defective gene in patients suffering from cystic fibrosis, genes encoding insulin, genes that compensate for the defective gene in patients suffering from ADA, and genes encoding factor VIII. *Id.*

The specification further teaches that the compounds that can be introduced into cells according to the methods defined by the present claims can be genetic constructs that include nucleic acid molecules that serve as genetic templates for therapeutic proteins *Id.* Such nucleic acid molecules include genes encoding cytokines, growth factors, chemokines, and toxins, including erythropoietin, interferon, LDL receptor, GM-CSF, IL-2, IL-4, and TNF. See page 13, lines 6 to 16 of the specification as filed. Such nucleic acid molecules, according to the specification, also include antibodies, HIV Vpr, TGFβ, and growth factors such as EPO, CSF, and GCSF. *Id.*

The specification further teaches that the compounds that can be introduced into cells according to the methods defined by the present claims can be genetic constructs that include nucleic acid molecules that serve as genetic templates for antisense molecules or that serve as genetic templates for ribozymes. See page 13, line 17 to page 14, line 16 of the specification as filed.

The specification describes the subject matter encompassed by the present claims because the specification describes the costimulatory ligands defined by the claims and describes a representative number of species of the compounds that can be introduced into cells according to the methods defined by the present claims. Accordingly, those skilled in the art would reasonably believe that Applicants were in possession of the subject matter defined by the present claims at the time of filing. The specification therefore contains an adequate written description of the claimed subject matter, and Applicants respectfully request withdrawal of the rejection.

Alleged Lack of Enablement

Claims 1 to 6 and 8 to 13 have been rejected under 35 U.S.C. § 112, first paragraph for lack of enablement because the specification allegedly fails to teach that the costimulatory ligands embraced by the claims promote targeted nucleic acid delivery. Applicants respectfully traverse the rejection because the Examiner has failed to establish a reasonable basis to question the enablement provided in the specification.

Preliminarily, as mentioned above, to further clarify the claimed subject matter,

claims 1 and 13 have been amended to recite that the costimulatory ligand comprises CD28 or a portion thereof. Support for the amendments is found in the specification, at, for example, page 24, lines 1 to 16.

The enablement requirement is met if the specification enables those of ordinary skill in the art to make and use the subject matter defined by the claims without undue experimentation. *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976). The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, whether it is undue. *Id.* Extensive experimentation is often necessary to practice inventions that involve unpredictable technologies, and such experimentation is not undue if the art typically engages in such experimentation. *PPG Indus., Inc. v. Guardian Indus. Corp.*, 75 F.3d 1558, 1564 (Fed. Cir. 1996). The Examiner bears the burden of establishing a reasonable basis to question the enablement provided for the claimed invention. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993).

The Office Action has failed to establish that those of ordinary skill in the art would have to engage in undue experimentation to practice the methods encompassed by the present claims. Specifically, the Office Action has not established that practice of the claimed methods would fail to result in targeted delivery of the compounds embraced by the claims. The Office Action asserts that "targeted gene deliver [*sic*] is still under development and highly unpredictable," and cites Deonarian, M.P., Expert Opin. Ther. Pat. 8:53-69 (1998) (hereinafter "the Deonarian reference"), U.S. Patent No. 6,103,521 (hereinafter "the Capon patent"), and U.S. Patent No. 5,741,492 (hereinafter "the Hurwitz patent") in support of the

proposition.

Contrary to the assertion made in the Office Action, the Deonarain reference does not support the proposition that targeted gene delivery is highly unpredictable. In fact, the reference states that vectors for targeted gene delivery containing a cell-specific ligand and a DNA coupling element "are able to deliver genes to cells in a receptor-specific manner, without any viral DNA sequences or packaging constraints. There are now many ligand/receptor systems under investigation, each one demonstrating successful gene transfer with a higher level of tissue specificity than viruses can offer." (Page 1).

In addition, the Capon patent also fails to demonstrate that targeted gene delivery is highly unpredictable because it is not directed to targeted gene delivery methods. The Capon patent describes chimeric receptors that contain a proliferation signaling domain and an effector function signaling domain (col 5, ln 44 - col 6, ln 43). The Capon patent states that DNA constructs encoding the chimeric receptors are introduced into target cells by any one of numerous means (col 14, lns 50-60), and further states that the binding of an extracellular inducer molecule to the chimeric receptor stimulates the host cells to act as therapeutic agents at the same time as they are expanding (col 15, ln 66 - col 16, ln 9). The Capon patent does not teach delivery of genes encoding the chimeric receptors to specific types of host cells, but merely states that numerous types of cells can be used as host cells (col 15, lns 8-24), and, therefore, is not directed to targeted gene delivery.

The Hurwitz patent similarly fails to demonstrate that targeted gene delivery is highly unpredictable because the Hurwitz patent is not directed to, nor does it address in any

manner, targeted gene delivery. The Hurwitz patent describes polyenv vaccines for human immunodeficiency virus (HIV) comprising a mixture of at lest 4-40 and up to 10,000 recombinant vaccinia viruses that each express a different variant of an HIV envelope protein (col 2, lns 42-60). The Hurwitz patent fails to teach or suggest that specific cells or types of cells are targeted by the vaccines, and, therefore, is not directed to targeted gene delivery methods.

The Deonarian reference and the Capon and Hurwitz patents, therefore, do not demonstrate that targeted gene delivery is highly unpredictable. Accordingly, the Examiner has failed to provide any evidence that reasons exist to doubt the objective truth of the teachings provided in the instant specification. The Office Action has therefore failed to establish that the present specification does not enable those of skill in the art to make and use the full scope of the subject matter defined by the present claims without undue experimentation. *In re Marzocchi*, 439 F.2d 220, 224 (C.C.P.A. 1971). Applicants accordingly request withdrawal of the rejection.

Alleged Anticipation

Claims 1 to 5, 8, 9, and 13 have been rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Horspool, *et al.*, *J Immunol* 160:2706-2715 (1998) (hereinafter "the Horspool reference"). Claims 1 to 5, 8, 9, 11, and 13 have been independently rejected under 35 U.S.C. § 102(a) as allegedly anticipated by Gherardi, *et al.*, *J Immunol* 162:6724-6733 (1999) (hereinafter "the Gherardi reference"). Applicants respectfully traverse the rejections because

the Horspool and Gherardi references each fail to disclose or suggest everyelement of the present claims.

The pending claims recite methods of introducing a compound into a cell that expresses costimulatory molecules comprising contacting the cell with a non-cellular particle that comprises the compound and a costimulatory ligand comprising CD28 or a portion thereof. The pending claims also recite methods of delivering a therapeutic protein to an individual comprising administering to tissue of said individual at a site on said individual's body a particle that comprises a nucleic acid molecule that encodes a therapeutic protein, and a costimulatory ligand comprising CD28 or a portion thereof.

The Horspool reference teaches coimmunization of mice with a plasmid encoding β-galactosidase and a plasmid encoding CD80 and also teaches coimmunization of mice with a plasmid encoding β-galactosidase and a plasmid encoding CD86 (Figure 5 and page 2707). The Gherardi reference teaches the inoculation of mice with vaccinia virus recombinants expressing HIV-1 Env and murine IL-12 genes or with vaccinia virus recombinants coexpressing both genes (Abstract). The Horspool and Gherardi references do not teach or suggest the claimed subject matter. Indeed, each reference does not teach or suggest methods of introducing a compound into a cell comprising contacting the cell with a non-cellular particle ***that comprises a costimulatory ligand*** as originally claimed, much less a costimulatory ligand comprising CD28 or a portion thereof. Furthermore, neither the Horspool nor the Gherardi reference teaches or suggests methods in which non-cellular particles comprising a costimulatory ligand are used to introduce compounds into ***cells that***

express costimulatory molecules.

Because the Horspool and Gherardi references each do not disclose or suggest these and other elements of the claims, the rejections for alleged anticipation should be withdrawn. *Atlas Powder Co. v. E.I. Du Pont de Nemours & Co.*, 750 F.2d 1569, 1574 (Fed. Cir. 1984)(holding of no anticipation affirmed because reference failed to disclose or suggest all claim elements).

Claims 1 to 4, 6, 9, 11, and 13 have been rejected under 35 U.S.C. § 102(a) as allegedly anticipated by U.S. Patent No. 6,319,504 (hereinafter "the Gallo patent"). Claims 1 to 6, 8, 9, 11, and 13 have been independently rejected under 35 U.S.C. § 102(e) as allegedly anticipated by U.S. Patent No. 6,342,372 (hereinafter "the Dubensky patent"). Applicants request reconsideration and withdrawal of the rejections because the disclosures of the Gallo and Dubensky patents each fail to disclose or suggest every limitation of the claims.

The Gallo patent teaches administration of nucleic acids comprising a sequence encoding β-hCG, or a β-hCG peptide, for the treatment or prevention of HIV infection. The Gallo patent states that the nucleic acid can be directly administered *in vivo* and can be administered in linkage to a ligand subject to receptor-mediated endocytosis. The Dubensky patent describes eukaryotic layered vector initiation systems that are capable of expressing a heterologous nucleic acid sequence in a eukaryotic cell transformed or transfected therewith. (col. 3, lns 57-60). The Dubensky patent further recites that the eukaryotic layered vector initiation system may be introduced into the target cells as a DNA-ligand complex that

includes the vector molecule (col. 8, ln 63-col. 9, ln 3). The Gallo and Dubensky patents each fail, however, to teach or suggest even a single ligand that could be used in the described methods, much less a ligand that comprise CD28 or a portion thereof. In addition, the Gallo and Dubensky patents each fail to teach or suggest that the DNA-ligand complex contains a costimulatory ligand that can be introduced into cells that express costimulatory molecules.

The Gallo and Dubensky patents, therefore, do not teach or suggest the claimed subject matter. Indeed, each patent does not teach or suggest methods of introducing a compound into a cell comprising contacting the cell with a non-cellular particle ***that comprises a costimulatory ligand*** as originally claimed, much less a costimulatory ligand comprising CD28 or a portion thereof. Furthermore, the Gallo and Dubensky patents each do not teach or suggest methods in which non-cellular particles comprising a costimulatory ligand are used to introduce compounds into ***cells that express costimulatory molecules.***

Although the Office Action asserts that "[the Dubensky patent teaches] that the vectors could be delivered as DNA-ligand complex along with polycation compound, and include immunomodulatory cofactors such as ICAM, LFA, B7, CD28 and CTLA-4" (Office Action dated March 1, 2002, page 12)(citations omitted), the Dubensky patent, in fact, does not teach that CD28 is an immunomodulatory cofactor that can be delivered along with the DNA-ligand complex and polycation compound (col 20, ln 43 to col 21, ln 67). Nor does the Dubensky patent teach or suggest that CD28 could be the ligand in the DNA-ligand complex.

In addition, although the Office Action asserts that "[the Dubensky patent teaches] targeting cells of macrophage (in Gaucher disease) or inducing T cell response via antigen

presenting cells (dendritic cells and macrophages)" (Office Action dated March 1, 2002, page 12)(citations omitted), the Dubensky patent does not teach or suggest that such cells are targeted by utilizing non-cellular particles that comprise a ***costimulatory*** ligand.

Because the Gallo and Dubensky patents each do not disclose or suggest every element of the present claims, the rejections for alleged anticipation should be withdrawn.

Conclusion

The claims are in condition for allowance, and an early Office Action to that effect is earnestly solicited.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 7, 9, and 14 to 31 have been cancelled.

The claims have been amended as follows.

1. (Amended) A method of introducing a compound into a cell that expresses costimulatory molecules, said method comprising contacting the cell with a non-cellular particle that comprises the compound and a costimulatory ligand comprising CD28 or a portion thereof.

2. (Amended) The method of claim 1 wherein the compound is a nucleic acid molecule ~~or protein~~.

4. (Amended) The method of claim 1 wherein the compound is DNA that comprises a nucleotide ~~sequences~~ sequence that encodes a protein operably linked to regulatory elements functional in the cell.

5. (Amended) The method of claim 1 wherein the compound is DNA that comprises a nucleotide ~~sequences~~ sequence that encodes an immunogenic protein operably linked to regulatory elements functional in the cell.

6. (Amended) The method of claim 1 wherein the compound is DNA that comprises a nucleotide ~~sequences~~ sequence that encodes an non-immunogenic protein operably linked to regulatory elements functional in the cell.

8. (Amended) The method of claim 1 wherein the cell that expresses costimulatory molecules is a dendretic cell or a macrophage ~~cell~~.

13. (Amended) A method of delivering a therapeutic protein to an individual comprising the step of administering to tissue of said individual at a site on said individual's body, a particle that comprises ~~therapeutic protein or~~ a nucleic acid molecule that encodes a therapeutic protein, and a costimulatory ligand comprising CD28 or a portion thereof.

New claims 32 to 42 have been added.